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Lindau Disease Treated by Bilateral Nephrectomy and Hemodialysis

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LINDAU DISEASE, also known as von Hippel-Lindau disease, is a hereditary disorder characterized by the association of cerebellar hemangioblastoma with any of several other visceral tumors.[1] These include retinal hemangioblastoma (the von Hippel tumor); spinal cord hemangioblastoma; pancreatic cysts; epididymal cysts and adenomas; pheochromocytoma, and renal angiomas, cysts, and carcinomas.[2] The diagnosis of Lindau disease depends on the demonstration of two hemangiomatous lesions in a single patient or the presence of a single lesion in a patient with a verified family history of the disease.

Renal cell carcinoma is present in approximately two thirds of patients affected with Lindau disease. It may be diagnosed clinically during life or appear as an incidental finding at autopsy.[2] Although Lindau originally believed that the renal tumors were always benign,[3] the metastatic potential of these neoplasms is now well documented.[4-6] Renal cell carcinoma is the cause of death in approximately a third of affected patients.[7] The typical tumor is multicentric in origin. An interval of several years may occur between resection of a hypernephroma in one kidney and the later appearance of tumor in the contralateral kidney.

Although a few patients with previous history of other types of renal malignancy have been accepted for dialysis,[8] little if any information is available regarding the suitability of patients with Lindau disease and renal carcinoma for hemodialysis. We present here the case of a patient with Lindau disease and bilateral renal carcinoma in whom bilateral nephrectomy and subsequent treatment with hemodialysis were carried out.

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Report of a Case

A 34-year-old white man was referred to San Francisco Veterans Administration Hospital in 1976 for evaluation of two months of increasing ataxia of gait. History showed that he had presented to another hospital in 1962 with similar symptoms and at that time had had resection of a cerebellar hemangioblastoma. Postoperatively he had had a persistent ataxic gait and weakness of the left arm and leg. His clinical status had remained unchanged for eight years when he again presented with increasing ataxia. Evaluation showed another cerebellar tumor which was felt to be unresectable. A course of treatment with radiation resulted in subsequent symptomatic improvement. He was again admitted to hospital two years later, when he presented after four weeks' experience of increasing headache, difficulty with vision and balance, and early morning nausea and vomiting. Bilateral carotid arteriograms showed a large cystic cerebellar lesion and two smaller cerebellar tumors. These tumors were excised, and the patient noted relief of his headaches, although the neurological deficits were unchanged.

His condition was then stable for the next three years, when the patient was again seen, this time with a two-week history of hematuria and right flank pain. On physical examination at that time, a palpable right kidney and an epididymal mass were discovered. An intravenous pyelogram showed a right renal mass and an arteriogram showed bilateral renal masses. During that period in hospital, excisional biopsy of the epididymal mass was accomplished, with a pathologic diagnosis of papillary cystadenoma. His symptoms resolved, and he was discharged. Two months later he was readmitted with a history of several days of hematuria and right flank pain. An intravenous pyelogram showed obstruction of the right ureter. The patient was observed and a follow-up pyelogram showed partial clearing of the obstruction, which at the time was attributed to the clot lysis. The patient's condition was then stable until the present admission.

Pertinent family history showed that the patient's mother had died at the age of 21 of a brain tumor.

On physical examination at the time of this admission, the patient was seen to be thin and had an obvious ataxic gait. Other neurological deficits included nystagmus on left lateral gaze, a slight weakness of the left upper and lower ex-

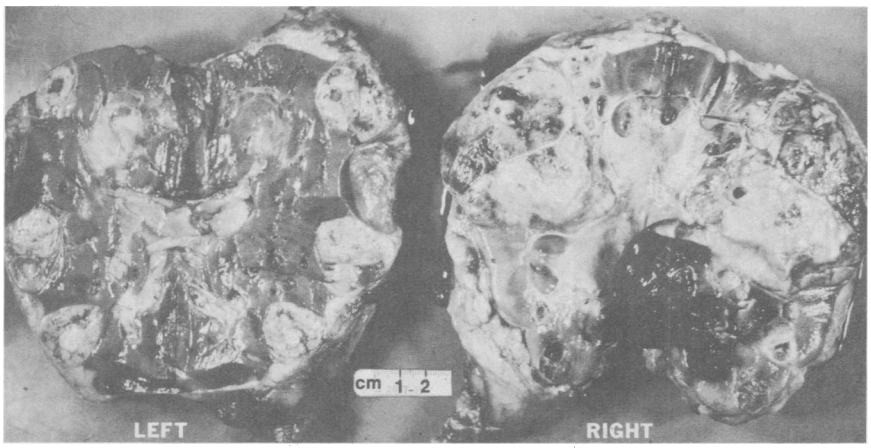

Figure 1.—Nephrectomy specimens from patient with Lindau disease and bilateral renal cell carcinoma. The left kidney has several foci of tumor, while the right kidney is extensively involved with malignant tissue.

tremities, and decreased sensation on the left side. Examination of the ocular fundi showed no evidence of retinal hemangiomata. On abdominal examination the right kidney was palpable. Laboratory values at time of admission included a hypochromic normocytic anemia with hematocrit of 28 percent. Serum erythropoietin level was 75 mU per ml (normal 7 to 36 mU per ml). An arteriogram showed bilateral renal masses, with extension of tumor into the right renal vein and inferior vena cava.

No evidence of distant metastatic disease was found after an extensive evaluation. A bilateral nephrectomy was done, including partial resection of the inferior vena cava. On pathologic examition of the kidneys (Figure 1), multiple bilateral renal carcinomas were found, with extension of tumor into the right renal vein and immediately adjacent portion of the vena cava. There was no indication that tumor extended through the renal capsule. Electron microscopy showed normal thickness of the glomerular basement membrane with no immune complex deposits.

Postoperatively regular hemodialysis was started. However, during the third hour of the second hemodialysis, the patient had a grand mal seizure. There was frequent recurrence of seizure activity during the next several days, with seizures occurring both late in dialysis and during the interdialytic period, before staff discovered that the patient had not actually been taking seizure medications. Thereafter, close supervision assured that he actually swallowed medications, and seizure activity ceased. Six months after initiation of hemodialysis three times a week, pericarditis developed, which responded promptly to treatment with indomethacin.

Seven months after initiation of hemodialysis, minimal ascites was observed on physical examination. Evaluation at that time included a paracentesis, with cytologic examination showing malignant cells. Cyclohexyl chlorethyl nitrosurea (CCNU) was then prescribed at 200 mg taken orally at intervals of six weeks, which he tolerated well. A year and a half after nephrectomy the patient is doing well on regular hemodialysis. He leads an active social life and participates in moderate activities, such as taking local sightseeing trips.

Discussion

This patient presented with many well-described manifestations of Lindau disease. The presenting symptoms of this entity are usually related to the cerebellar or retinal tumors[2] and may include headache, vertigo and emesis. Distinction is usually made between Lindau disease and Lindau tumor. "Lindau tumor" is used as an eponym for cerebellar hemangioblastoma, while "Lindau disease" is used for the association of this cerebellar tumor with visceral tumors. Cerebellar hemangioblastomas may account for 2 percent of all brain tumors and 7 percent of all posterior fossa tumors.[9] Such tumors represent a major source of early morbidity in patients with Lindau disease, often causing disabling neurological manifestations with occasional fatal complications.[1] Although these tumors are characteristically cystic with a mural nodule, a fourth to a third of them may be solid.

Although neurological manifestations are usually the major initial symptoms in Lindau disease, renal lesions are common and are a major cause of both morbidity and late mortality.[7] In one series of 11 patients with Lindau disease, nine had cysts or tumors (or both) involving the kid-

ney,[9] while in a series of several families with Lindau disease,[7] half of the patients with renal cell carcinoma had metastatic disease. Renal cell carcinoma associated with Lindau disease appears to differ somewhat from sporadic hypernephroma in the earlier age at diagnosis, the tendency toward multicentric origin and the lack of male predominance.

There is no available information about a possible increased incidence of neurological complications of dialysis in those patients with a previous history of resected cerebellar tumors. Complications in this group of patients might include an increased incidence of either dialysis disequilibrium syndrome with seizures or intracerebral bleeding, the latter due to repeated heparin administration required for hemodialysis. In the case reported here, the initial seizures may have been a manifestation of dialysis disequilibrium syndrome, but they also may have been due, at least in part, to failure to take seizure medication. He has been seizure-free since this was corrected and there has been no clinical evidence of intracerebral bleeding after more than a year and a half of regular hemodialysis. This patient has had no unusual complications of hemodialysis due to the preexisting cerebellar tumors and neurosurgical procedures. Based on this information, we believe that patients with Lindau disease and bilateral renal carcinoma should be considered as candidates for hemodialysis. However, it is imperative that this decision be made early in order to avoid the more extensive morbidity of metastatic disease.

Renal cell carcinoma is among the leading causes of death in patients with Lindau disease.[7] Improvement in prognosis of patients with Lindau disease and renal cell carcinoma will depend on earlier detection and treatment of the several treatable manifestations of this disease. Christoferson and coworkers[10] studied 90 members of an affected family and noted a 12 percent incidence of the combination of cystic and angiomatous lesions. They suggested that the trait is inherited in a modified dominant pattern with incomplete penetrance. Silver and Providence[11] reported an even higher incidence (80 percent to 90 percent penetrance) in a retrospective study of a large affected family.

Melmon and Rosen[2] advocated screening of affected kindreds. Removal of hemangioblastomas from the central nervous system, detection and treatment of retinal hemangioblastomas before visual acuity is decreased, and genetic counseling are reasonable steps to decrease morbidity in this disease. In addition, renal cell carcinoma associated with Lindau disease should be excised early before complications due to metastatic disease can occur.

With earlier diagnosis and improved methods of treatment of the cerebellar tumors in this disease, it is likely that more patients will survive long enough for renal carcinomas to develop. These renal tumors will often ultimately be bilateral and, therefore, a decision will be required as to suitability of the patient as a hemodialysis candidate.

Summary

A 34-year-old man presented with several manifestations of Lindau disease, including bilateral renal cell carcinomas. He also had a previous history of neurosurgical procedures and radiation therapy for recurrent cerebellar tumors. A bilateral nephrectomy was done, and the patient was placed on regular hemodialysis. He has had no unusual complications of hemodialysis during a year and a half of treatments three times each week. Although the initial symptoms of Lindau disease are usually due to cerebellar tumors, renal cell carcinoma is often a major cause of late morbidity. With improved treatment of the cerebellar tumors, it is likely that more patients with Lindau disease will survive and that renal carcinoma will develop subsequently. Patients with Lindau disease and bilateral renal cell carcinoma should be considered as hemodialysis candidates. This decision should be made early before metastasis has occurred.

REFERENCES

1. Grossman M, Melmon KL: Von Hippel-Lindau disease, *In* Vinken PS, Bruyn GW (Eds): Handbook of Clinical Neurology, Vol XIV. Amsterdam, North-Holland Publishing Co, 1972, p 241

2. Melmon KL, Rosen SW: Lindau's disease. Am J Med 36: 595-617, Apr 1964

3. Lindau A: Discussion on vascular tumors of the brain and spinal cord. Proc Roy Soc Med 24:363-387, 1931

4. Goodbody RA, Gamlen TR: Cerebellar haemangioblastoma and genitourinary tumours. J Neurol Neurosurg Psychiatry 37:606-609, May 1974

5. Kaplan C, Sayre GP, Greene LF: Bilateral nephrogenic carcinomas in Lindau-Von Hippel disease. J Urol 86:36-42, 1961

6. Kranes A: Case records of the Massachusetts General Hospital: Case 47:1966. N Engl J Med 275:950-956, 1966

7. Horton WA, Wong V, Eldridge R: Von Hippel-Lindau disease: Clinical and pathological manifestations in nine families with 50 affected members. Arch Intern Med 136:769-777, Jul 1976

8. Matas AJ, Simmons RL, Buselmeier TJ, et al: Successful renal transplantation in patients with prior history of malignancy. Am J Med 59:791-795, Dec 1975

9. Olivecrona H: The cerebellar angioreticulomas. J Neurosurg 9:317-330, 1952

10. Christoferson LA, Gustafson MB, Petersen AG: Von Hippel-Lindau's disease. JAMA 178:280-282, 1961

11. Silver ML, Providence RI: Hereditary vascular tumors of the nervous system. JAMA 156:1953, 1954